Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Di Stasi A, Tey S-K, Dotti G, et al. Inducible apoptosis as a safety switch for adoptive cell therapy. N Engl J Med 2011;365:1673-83.

Supplementary Appendix

Supplement to: Inducible Apoptosis as a Safety Switch for Adoptive Cell Therapy

Supplementary Appendix Table of Contents

METHODS

Study site and outline.

The clinical trial was approved by the US Food and Drug Administration, the Recombinant DNA Advisory Committee and the Institutional Review Board of Baylor College of Medicine. All participants gave informed consent on enrollment and pre-infusion. Five patients received iCasp9 allodepleted cells between 30 and 90 days following CD34+ haploidentical-stem-cell-transplantation, at doses ranging from $1x10^6$ to $1x10^7$ cells/kg. Cryopreserved T cells were thawed and infused at the Center for Cell and Gene Therapy in The Methodist Hospital or Texas Children's Hospital. Patients who developed GvHD after infusion of allodepleted T cells received 0.4 mg/kg of the dimerizing agent AP1903 (Bellicum Pharmaceuticals, Inc.) as a 2-hour infusion.[1]

Assay methods

Proliferation assay. Proliferation assays were performed as previously described.[2,3] Briefly, control PBMC, and cells cultured for 4 days with or without CD25 immunotoxin, were plated in triplicate in U-bottom 96-well plates (Nunc, Rochester, NY). After 2 days, cultures were pulsed with 0.037 MBq (1 μCi) ^{3}H-thymidine per well (Amersham Biosciences, Piscataway, NJ) and harvested onto glass fiber strips 18 hours later using a Brandel PHD cell harvester. ^{3}H-thymidine uptake was measured using a liquid scintillation counter (Perkin Elmer TR2910) and the percentage of residual proliferation was evaluated as follows: counts in anti CD25 treated cells (co-culture - PBMC) ÷ counts in non treated controls (co-culture - PBMC) x 100. Allodepletion was considered adequate if the residual

CD3+CD25+ population was <1% as measured by Flow cytometry and residual proliferation was <10% as measured by ^{3}H thymidine incorporation.[2,3]

TCR Vβ analysis by spectratyping

Spectratyping analysis was performed by the FHCRC immune monitoring lab as previously described.[4] The amplified PCR products were size fractionated by capillary gel-electrophoresis. The dye labeled PCR products and GeneScan-500 ROX DNA size marker (Applied Biosystems) were analyzed using 36cm array on an ABI model 3730xl DNA sequencer. The GeneScan data was analyzed using the GenMapper software v4.0 (Applied Biosystems).

IFN-γ ELIspot assay.

The IFN-γ ELIspot assay was performed as previously described[2,3]. $2x10^{5}$ patients' PBMCs/well were plated in duplicate and stimulated overnight with 1ng/µl overlapping peptide libraries (15-mer peptides overlapping by 11 amino acids) derived either from an irrelevant antigen (HCV core antigen) or the 2A sequence[5,6] (JPT Technologies (Berlin, Germany). As positive control, T cells were stimulated with 25 ng/mL phorbol myristate acetate (PMA) and 1 µg/mL ionomycin (Iono; Sigma-Aldrich, St Louis, MO). IFN-γ^{+} SFC were enumerated (Zellnet Consulting, Fort Lee, NJ).

ADV quantitative PCR

ADV qPCR was performed by Viracor IDT Laboratories, on patient stool specimes using primers and probes specific for all the 52 serotypes of ADV.

Details of *iCasp*9 Construct

The F36V mutation in the single FKBP domain of the *iCasp*9 construct increases the binding affinity of FKBP12 to the synthetic homodimerizer AP20187 or AP1903.[7] The caspase recruitment domain (CARD) has been deleted from the human caspase-9 sequence because its physiological function has been replaced by FKBP12, and its removal decreases basal caspase activity[8,9] The 2A-like sequence encodes a 20 amino acid peptide from the *Thosea asigna* insect virus ensures the expression of the two separate transgenes.[5,6] *ΔCD19* is derived from full-length *CD19* (GenBank NM 001770), truncated at amino acid 333 (TDPTRRF), which shortens the intracytoplasmic domain from 242 to 19 amino acids, and removes all conserved tyrosine residues that are potential sites for phosphorylation.[10] A stable PG13 clone producing Gibbon ape leukemia virus (Gal-V) pseudotyped retrovirus was made by transduction with vector supernatant obtained by transient transfection of the Phoenix Eco cell line (ATCC product #SD3444; ATCC, Manassas, VA) with *SFG.iCasp9.2A.ΔCD19*. A master cell-bank was generated, and all batches of retroviral supernatant were tested to exclude the presence of replication competent retrovirus (RCR) and issued with a certificate of analysis as directed by our SOPs.

Details of Retroviral Transduction

To activate the allodepleted T cells, non-tissue culture-treated flasks (Nunc, Rochester, NY) were coated with 1μg/ml of OKT3 and incubated overnight at 4°C. Allodepleted cells were added at 2-5×10^7 cells per flask. At 24 hours, 100 U/ml of recombinant human interleukin-2 (IL-2; Proleukin; Chiron, Emeryville, CA) were added. Retroviral transduction was performed at 48 hours after activation. Non-tissue culture-treated T75 flasks (Nunc, Rochester, NY), were coated with recombinant fibronectin fragment (CH-296;Retronectin; Takara Mirus Bio, Madison, WI) (70 μg in 10 ml of phosphate buffered saline 1x (Sigma, St Louis, MO) at 4°C. The following day, flasks were loaded with 10 ml of retroviral vector-containing supernatant and incubated 1-3 hours at 37° C, after which OKT3-activated cells were added at 1-4 x 10^7 cells per flask in fresh retroviral vector-containing supernatant and T-cell culture medium supplemented with 100 U/ml IL-2. Cells were harvested the following morning and expanded in tissue-culture- treated T75 or T175 flasks in culture medium supplemented with 50 to 200U/ml IL-2 at a seeding density of 5 to 8×10^5 cells/ml. CD19 selection was performed four days after transduction as described in the text.[11]

Table S1 A. Basic phenotype

Patient No.	Sample	Total $CD3^+$ (%)	$CD3^+$ $CD19^+$ (%)	$CD4^+$ $CD19^+$ (%)	$CD8^+$ $CD19^+$ (%)	$CD20^+$ (%)	$CD3^-$ $CD56^+CD16^+$ (%)	$CD3^-$ $CD56^+CD16^+$ $CD19^+$ (%)	*iCasp9* transgene copies/µg of DNA
P1	Cell line	98.8	63.0[a]/92.0[b]	29.2	62.8	0.2	0.8	0.3	$5.40x10^5$
	PB Pre AP1903	40.0	36.5	34.0	2.5	20.5	21.6	0.4	$1.74x10^5$
	PB Post AP1903	29.0	11.0	10.4	0.6	7.7	47.0	0.3	$0.43x10^5$
P2	Cell line	95.7	46.0[a]/90.0[b]	17.8	72.2	0.1	2.7	1.3	$7.90x10^5$
	PB Pre AP1903	40.6	23.0	10.2	12.8	26.1	30.0	3.4	$0.87x10^5$
	PB Post AP1903	23.2	2.91	0.3	2.5	37.4	34.4	0.4	$0.10x10^5$
P3	Cell line	97.5	65.0[a]/93.0[b]	29.3	63.7	0.4	1.2	0.7	$6.70x10^5$
	PB M1	40.4	0.5	0.2	0.3	17.9	37.8	0.0	$0.16x10^5$
P4	Cell line	95.7	64.0[a]/91.0[b]	19.3	71.7	0.3	2.7	1.3	$7.00x10^5$
	PB Pre AP1903	43.2	23.3	4.5	18.8	3.01	48.0	**0.0**	$0.65x10^5$
	PB Post AP1903	11.2	2.4	0.9	1.5	11.2	46.7	0.0	$0.10x10^5$
P5	Cell line	90.5	43.0[a]/90.0[b]	22.2	67.8	0.0	10.4	5.6	$5.10 x10^5$
	PB Pre AP1903	30.3	28.1	19.5	8.58	28	37.5	4.4	$0.46x10^5$
	PB Post AP1903	5.6	2.6	0.8	1.83	8.5	80.0	0.8	$0.18x10^5$

Table S1B. Memory markers

Patient No.	Sample	$CD3^+$ $CD19^+/\mu L$	Naïve	EM RA	CM	EM
			$CD3^+CD19^+$ $CD45RA^+$ $CD62L^+$ *(%)*	$CD3^+CD19^+$ $CD45RA^+$ $CD62L^-$ *(%)*	$CD3^+CD19^+$ $CD45RO^+$ $CD62L^+$ *(%)*	$CD3^+CD19^+$ $CD45RO^+$ $CD62L^-$ *(%)*
P1	Cell line		1.1	6.2	22.3	70.4
	PB Pre AP1903	348.0	0.1	0.0	82.9	1.0
	PB Post AP1903	154.0	1.3	1.9	26.7	70.0
P2	Cell line		0.4	5.9	15.6	78.0
	PB Pre AP1903	236.0	4.1	11.7	46.4	37.9
	PB Post AP1903	41.0	3.6	14.1	47.0	35.2
P3	Cell line		0.1	3.6	6.7	89.5
	PB M1	8.0	15.9	43.1	3.2	37.8
P4	Cell line		0.1	3.6	6.2	89.9
	PB Pre AP1903	122.0	7.1	29.4	13.1	50.4
	PB Post AP1903	18.0	7.3	11.2	49.0	32.0
P5	Cell line		0.1	5.3	3.3	91.2
	PB Pre AP1903	155.0	3.2	2.7	88.3	5.9
	PB Post AP1903	64.0	2.3	3.9	33.6	60.1

Table S1C. Activation markers

Patient No.	Sample	WBC	Ly	$CD3^+$ $CD19^+$	$CD3^+$ $CD19^+$				
					$CD25^+$	$CD69^+$	$CD27^+$	$CD28^+$	$CD127^+$
		$X10^3$ /μL	(%)	(%, Ly gate)	(%)				
P1	Cell line			92.0	91.5	2.1	49.0	97.0	83.0
	PB Pre AP1903	5.6	16.8	36.5	37.6	2.0	65.0	99.0	86.0
	PB Post AP1903	6.8	20.6	11.0	7.4	4.8	45.8	90.0	16.5
P2	Cell line			90.0	86.0	3.9	13.3	98.0	53.0
	PB Pre AP1903	4.0	25.3	23.0	11.5	3.5	33.0	65.0	38.0
	PB Post AP1903	7.1	19.7	2.91	1.6	2.1	40.0	67.0	46.0
P3	Cell line			93.0	91.0	2.6	15.7	97.0	45.0
	PB M1	3.8	35.0	0.6	6.5	15.4	52.9	35.0	84.0
P4	Cell line			91.0	90.4	5.3	31.4	97.8	73.0
	PB Pre AP1903	2.9	18.0	23.0	13.6	3.0	24.0	52.0	5.0
	PB Post AP1903	2.7	28.0	2.4	23.0	19.7	72.0	90.0	26.0
P5	Cell line			90.0	20.7	8.0	23.0	37.6	57.0
	PB Pre AP1903	3.8	14.0	28.1	54.6	8.9	46.0	92.0	6.0
	PB Post AP1903	5.0	48.0	2.65	22.0	15.0	66.0	91.0	25.0

Table S1 A, B and C: Lineage, memory and activation phenotype of transduced T cells.

Phenotypes of the CD3+CD19^{+} cell lines prior to infusion, as well as patient peripheral blood immediately prior to and 7-9 days after administration of the AP1903 dimerizing drug (P1,2,4,5) or at 1 month after T-cell infusion (P3, who did not receive the AP1903 dimerizing drug) are shown. Cells were analyzed by fluorescence-activated cell sorting after staining with CD3 and CD19 together with (A) lineage markers; CD4, CD8, CD16, CD20, CD56 antibodies (all from Becton Dickinson); (B and C) activation and memory markers; CD45RA, CD45RO, CD62L antibodies (Beckman Coulter) and CD25, CD27, CD28, CD69, CD127 antibodies (all from Becton Dickinson). We used monoclonal antibodies conjugated with phycoerythrin (PE), fluorescein isothiocyanate (FITC), peridinin chlorophyll protein (PerCP) or allophycocyanin (APC) APC-Alexa Fluor750, energy coupled dye. A nontransduced control was used to set the negative gate for CD19. *[a] before cliniMACS selection; [b] after cliniMACS selection; EM: effector memory; EM RA: Terminally differentiated effector memory; CM: central memory. WBC: white blood cells; Ly: lymphocytes; PB: peripheral blood.*

Table S2. CBC before and after AP1903

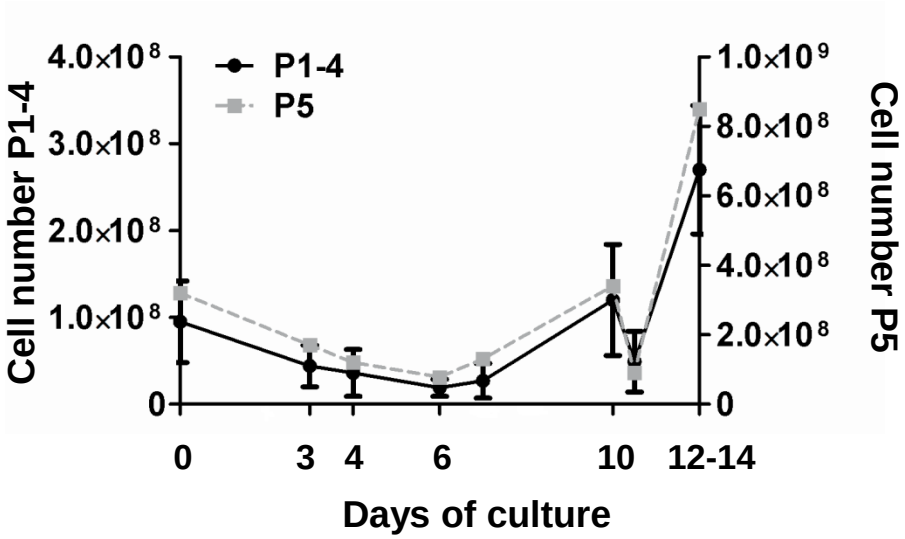
Patient No.	AP1903 timeline	*WBC 10^3/µl*	*ANC 10^3/µl*	*Ly 10^3/µl (%)*	*Hgb g/dl*	PLT *10^3/µl*
P1	*Before*	5.27	3.86	0.74 *(14.2)*	8.9	57
	+2d post	4.12	2.72	0.48 *(11.7)*	10.1	46
P2	*Before*	3.89	2.05	0.76 (19.6)	10.9	171
	+2d post	5.01	4.24	0.50 (10.0)	10.9	197
P4	*Before*	2.95	1.69	0.29 (10.1)	9.8	27
	+2d post	3.36	1.90	0.78 (23.5)	9.6	28
P5	*Before*	3.81	3.07	0.38 (10.1)	10.4	71
	+2d post	2.70	1.95	0.36 (13.4)	9.3	68

Table S2: Complete blood counts (CBC) before and after AP1903 administration.

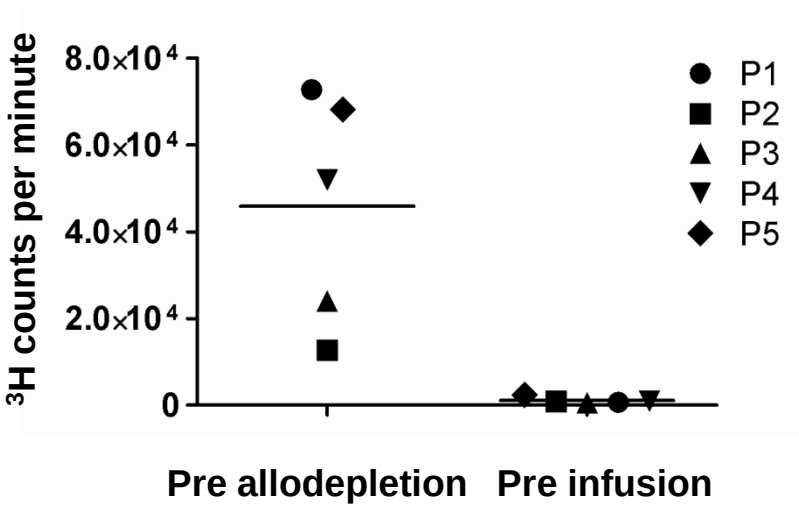
The Table reports the complete blood count values before and 2 days after AP1903 administration demonstrating that the dimerizing drug had no effect on cell subpopulations/counts other than $CD3^{+}CD19^{+}$ infused T cells.

CBC: complete blood count: WBC: white blood cells; ANC: absolute neutrophils count; Ly: lymphocytes; Hgb: hemoglobin; PLT: platelets.

A



B



C

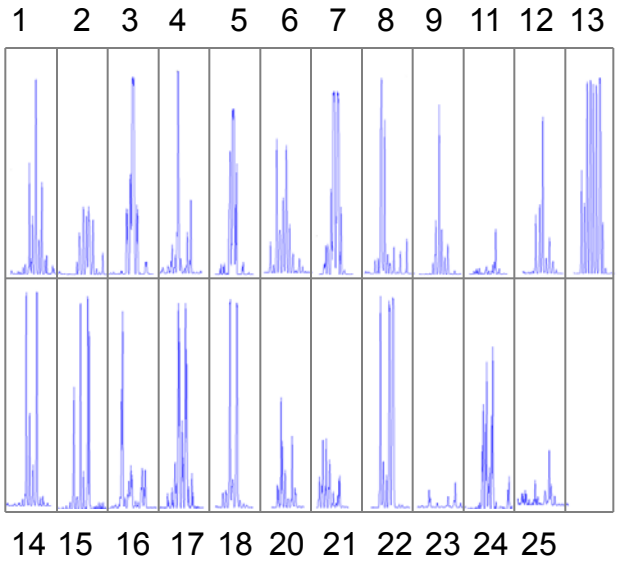
Day of culture		0	3	4	6	10	10	12 to 14
		Alloactivation		Allodepletion	Transduction	Pre selection	Post selection	Cryopreservation
P1-4 (dose level 1-2)	Cell number, *mean*	9.5E+07	4.4E+07	3.6E+07	1.9E+07	1.2E+08	4.9E+07	2.7E+08
P5 (dose level 3)	Cell number	3.2E+08	1.7E+08	1.2E+08	7.8E+07	3.4E+08	9.0E+07	8.5E+08
Viability *(trypan blue)*	Mean± SD	N/A	97.6±0.5	95±1.9	97.6±0.5	97.4±0.9	96.8±2.7	98±1

Fig S1

Figure S1: Phenotype, alloreactivity and expansion of manufactured cell lines. (A,C) Cell number and viability during manufacture of the infused cell lines (B) Scatter plot showing allospecific proliferation of all 5 patients' cell lines in response to stimulation with recipient cells before and after allodepletion (pre-infusion) as measured by ^{3}H thymidine incorporation (counts per minute (c.p.m) values).These data show no evidence for retention or selection of alloreactive cells following our depletion/transduction protocol. They are also consistent with the incidence of Grade I GvHD shown in Figure 2, which matches that observed in our previous studies of identical allodepletion without transduction[11] and with the absent of Grade II or higher GvHD even in subject 5 who received haploidentical allodepleted T cells at 10^{7} /kg.

A

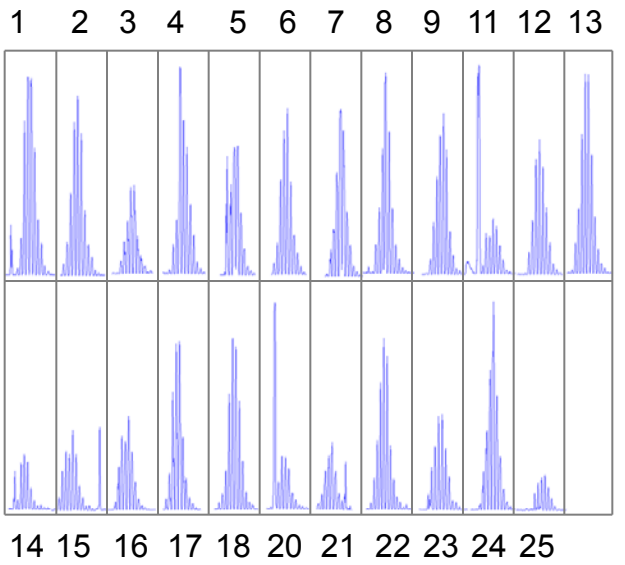
TCR Vβ



P2

Pre AP1903

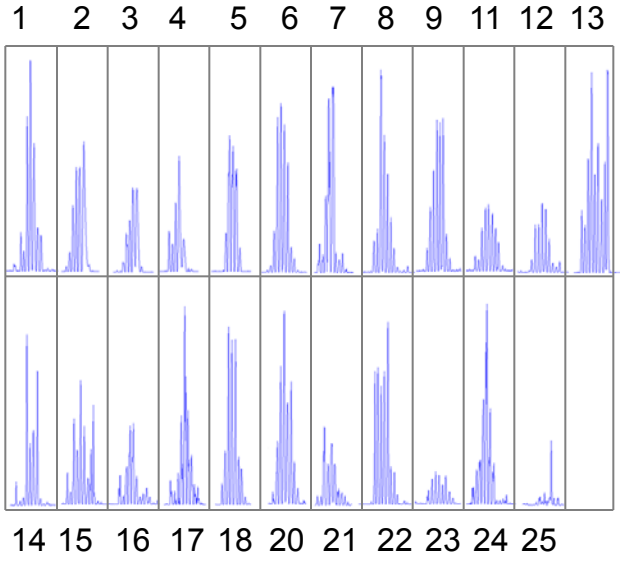
1 mo post T-cell



P3

No AP1903

9 mo post T-cell



P2

Post AP1903

5 mo post T-cell

TCR Vβ

Fig S2A

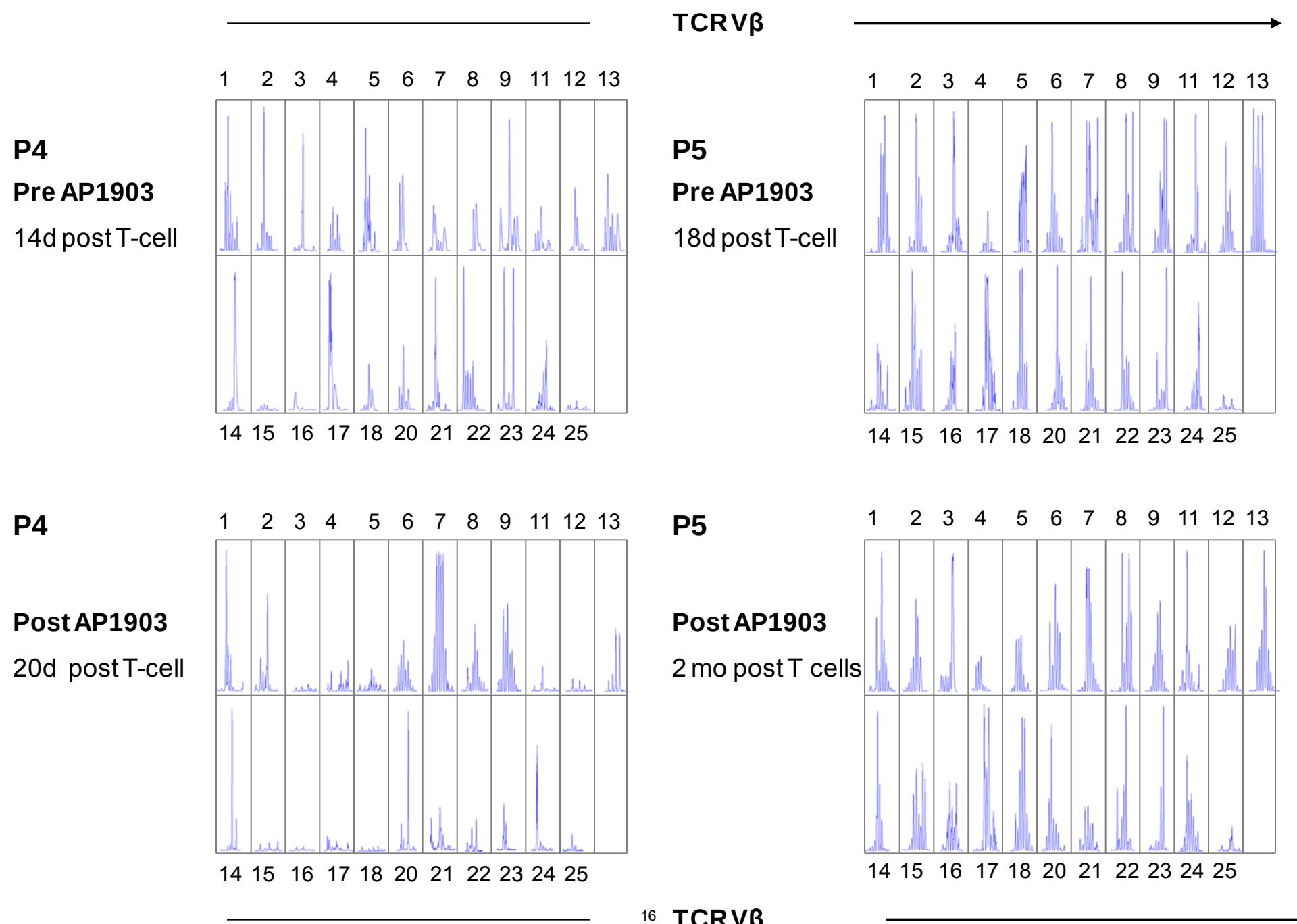


Fig S2A (cont'd)

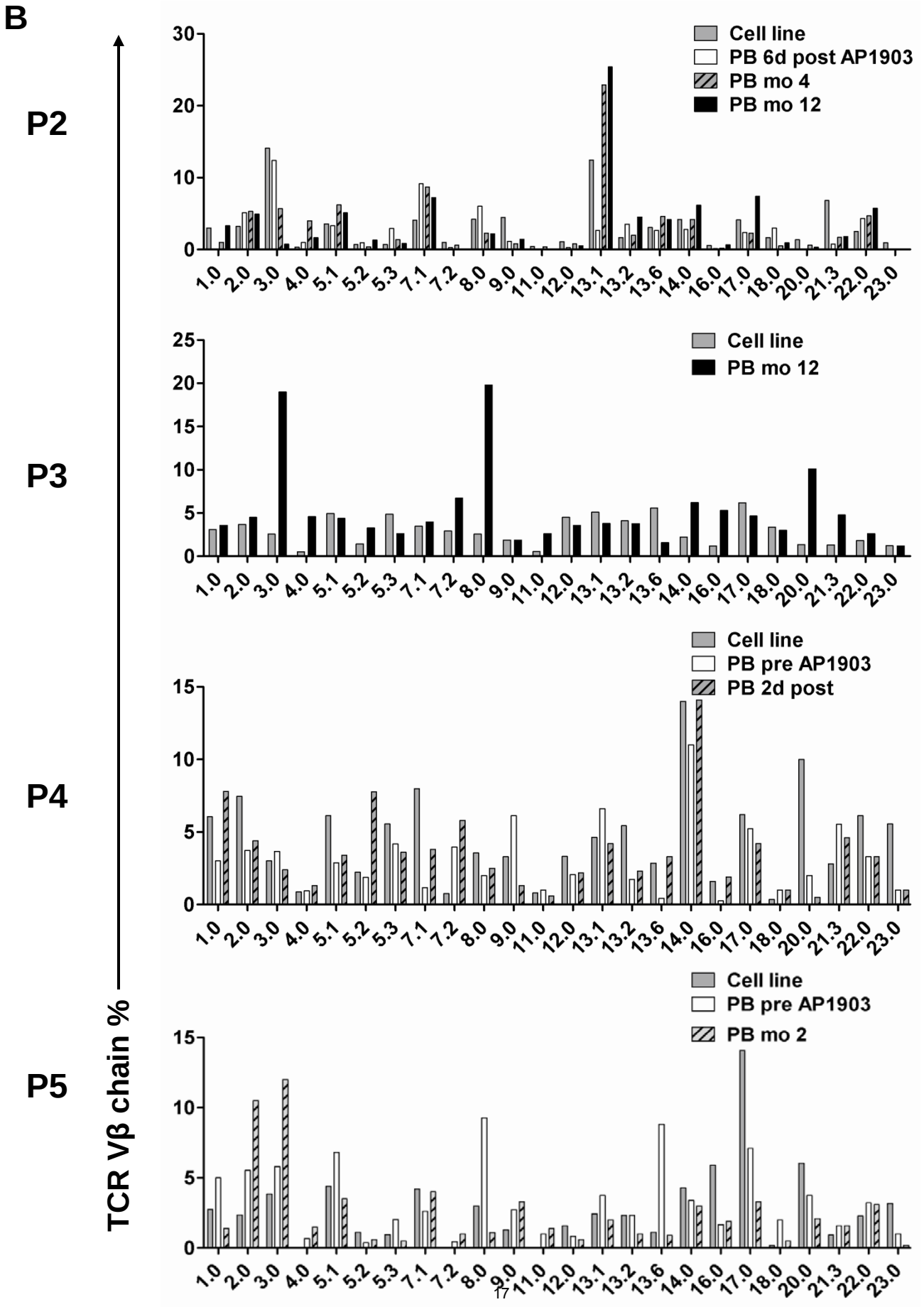

B
P2
Cell line
PB 6d post AP1903
PB mo 4
PB mo 12
P3
Cell line
PB mo 12
P4
Cell line
PB pre AP1903
PB 2d post
P5
Cell line
PB pre AP1903
PB mo 2
TCR Vβ chain %
1.0 2.0 3.0 4.0 5.1 5.2 5.3 7.1 7.2 8.0 9.0 11.0 12.0 13.1 13.2 13.6 14.0 16.0 17.0 18.0 20.0 21.3 22.0 23.0
TCR Vβ chain

Fig S2B

Figure S2: $CD3^+CD19^+$ T cells have polyclonal TCR Vβ expression after AP1903 administration.

Total and Transgenic T cell Reconstitution remains polyclonal after administration of dimerizing drug.

After infusion of icasp9 T cells, the peripheral blood CD3+ T cells (including the CD3+CD19+ subset) are polyclonal, and they remain so after dimerizing drug administration.

A) Spectrotyping analysis for repertoire of TCR Vβ families is shown for P2,4 and 5 before and at the indicated time points after AP1903 administration, and for P3, who did not develop GvHD.

B) Patient PBMCs were analyzed for TCR Vβ chain repertoire using a panel of monoclonal antibodies (IO Test Beta Mark kit, Beckman Coulter). Repertoire was determined on the CD3+CD19+ T cell gate immediately prior to administration of AP1903 and at the indicated timepoints after AP1903 (P2,4 and 5), and at 12 months after T-cell infusion in P3 who did not develop GvHD.

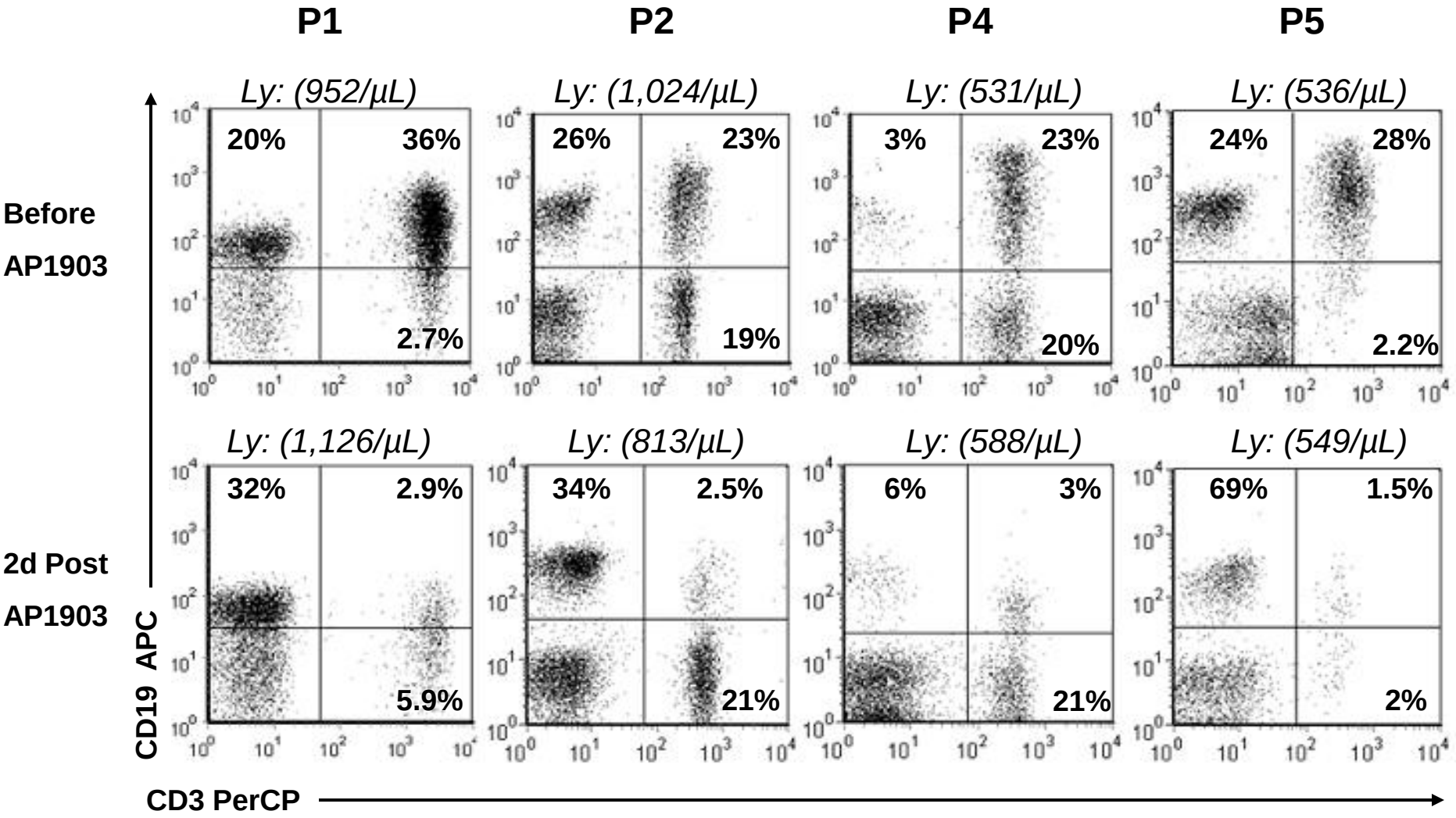

P1
P2
P4
P5
Ly: (952/µL)
Ly: (1,024/µL)
Ly: (531/µL)
Ly: (536/µL)
20%
36%
2.7%
26%
23%
19%
3%
23%
20%
24%
28%
2.2%
Before AP1903
Ly: (1,126/µL)
Ly: (813/µL)
Ly: (588/µL)
Ly: (549/µL)
32%
2.9%
5.9%
34%
2.5%
21%
6%
3%
21%
69%
1.5%
2%
2d Post AP1903
CD19 APC
CD3 PerCP

Figure S3

Figure S3. CD19 expression in $CD3^+$ cells before and after administration of Dimerizing drug

Following exposure to dimerizing drug in vivo, the majority of $CD3^+CD19^+$cells are eliminated (see figure 2), but as shown in this supplementary figure, a small proportion of the $CD19^-$ low expressing $CD3^+$ cells are preferentially spared. This phenomenon of preferential removal of the highest expressing cells may allow selective removal of (activated) alloreactive T cells that are causing GvHD whilst sparing (unstimulated) virus reactive cells for future expansion and reconstitution, since increased T cell expression of retrovirally transduced transgenes is favored by cell (allo)activation (Refs #16 Tey et al 2007 and #27, Karen et al 1999). (see also figures 3 &4 and S4). *Ly/µl: lymphocytes per µl of peripheral blood.*

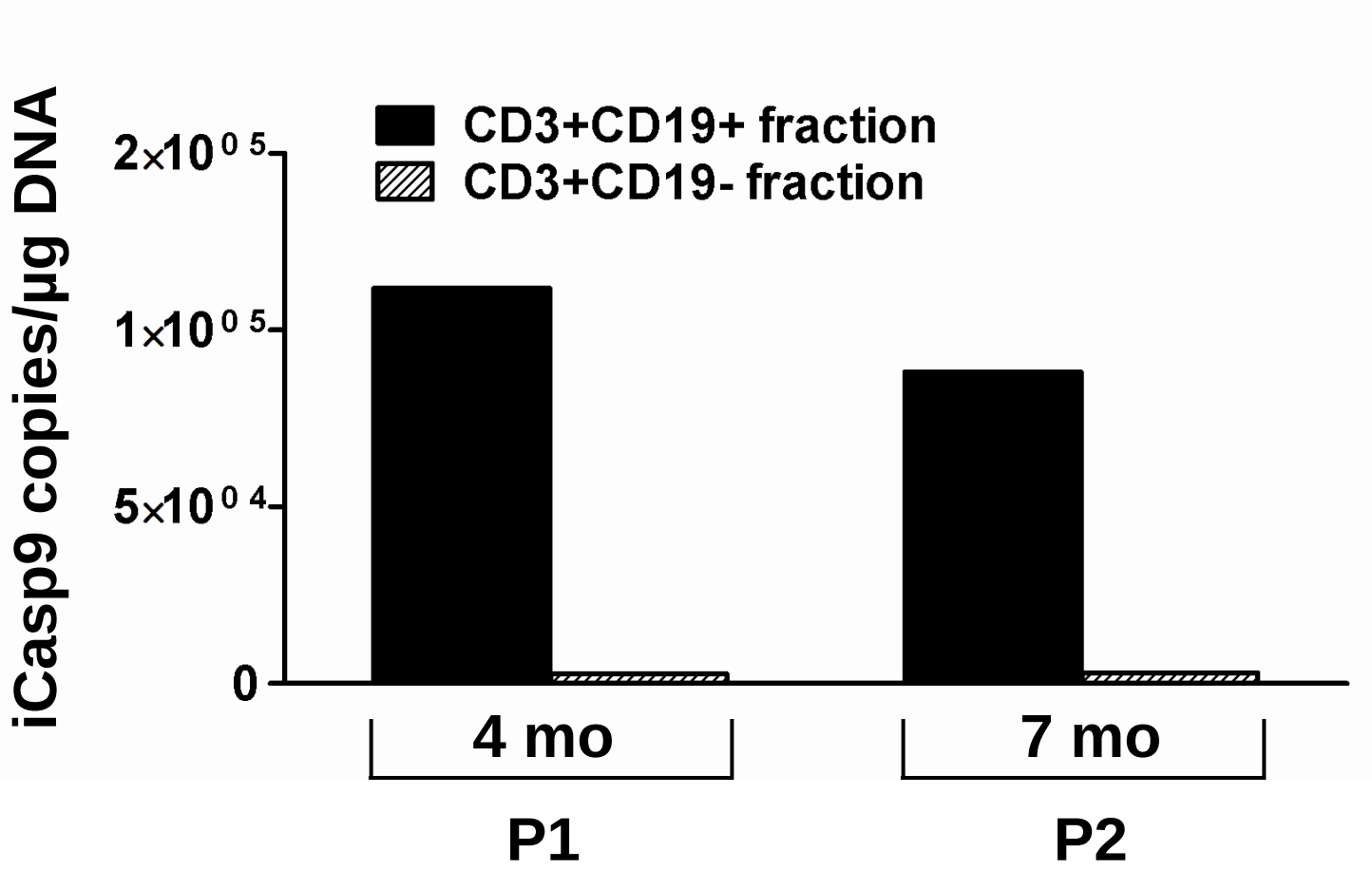

iCasp9 copies/µg DNA
2×10^05
1×10^05
5×10^04
0
CD3+CD19+ fraction
CD3+CD19- fraction
4 mo
7 mo
P1
P2

Fig S4

Figure S4. iCasp9 signal in $CD3^+CD19^+$ and $CD3^+$ $CD19^-$ subsets

As shown in Figure 2, by 24 hours after administration of dimerizing drug there is significant reduction in transgenic cells measured by either by reduction in $CD3^+CD19^+$ dual positive cells or by levels of icasp9 transgene measured by QPCR.). After extraction (Qiagen), DNA was amplified in triplicate with primers and TaqMan probe (Applied Biosystems, Foster City, CA), which are specific for the *iCasp9* sequence, using the ABI PRISM® 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). To generate DNA standards, we established serial dilution of the DNA plasmid encoding *iCasp9.2A.⊿CD19.*

In figure 2, the reduction in the QPCR signal is slightly but consistently greater than the reduction in the number of $CD3^+CD19^+$ dual positive cells (circa 93% versus circa 99%). To discover if some transgenic cells are $CD3^+CD19^-$ but are nonetheless iCasp9 transgene positive, we directly measured the association between QPCR signal for iCasp9 transgene and expression of the phenotypic marker for CD19 from the tandem construct shown in Figure 1. QPCR for iCasp9 transgene was performed on $CD3^+$ $CD19^+$ and $CD3^+$ $CD19^-$ FACS sorted populations (MOFlow; Beckman-Coulter) after staining with CD3FITC and CD19 PE monoclonal antibodies (BD Biosciences). As shown, iCasp9 signal in the $CD3^+CD19^-$ population was only 3 percent of that in the $CD3^+CD19^+$ population, confirming the results in Figure 2 by showing that the great majority of cells that are *iCasp9* transgene positive also express the $CD19^+$ phenotypic marker.

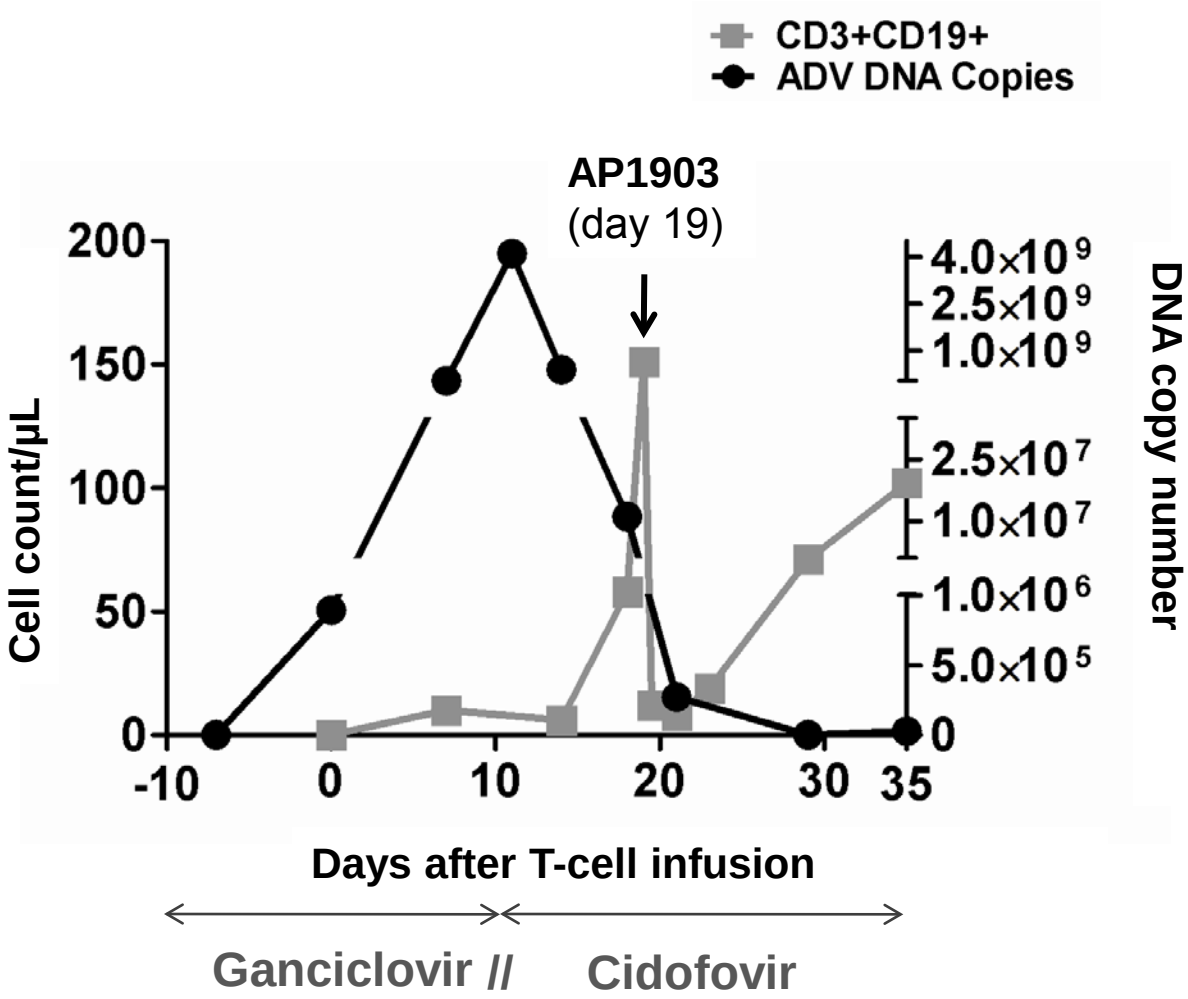

CD3+CD19+
ADV DNA Copies
AP1903
(day 19)
Cell count/μL
DNA copy number
200
150
100
50
0
4.0×10⁹
2.5×10⁹
1.0×10⁹
2.5×10⁷
1.0×10⁷
1.0×10⁶
5.0×10⁵
0
-10
0
10
20
30
35
Days after T-cell infusion
Ganciclovir //
Cidofovir

Fig. S5

Figure S5: $CD3^+CD19^+$ T cell engraftment is associated with control of adenovirus infection (measured as adenovirus DNA) and resolution of gastrointestinal symptoms.

P5 had an ADV infection and diarrhea refractory to ganciclovir treatment. The figure illustrates the rise in $CD3^+CD19^+$ T cells count/µl of blood co-incident with a decline in adenovirus genomes in stool as evaluated by Q-PCR. These findings co-incided with the presence of adenovirus-specific T cells in peripheral blood as shown in Figure 4D and with the resolution of gastrointestinal symptoms.

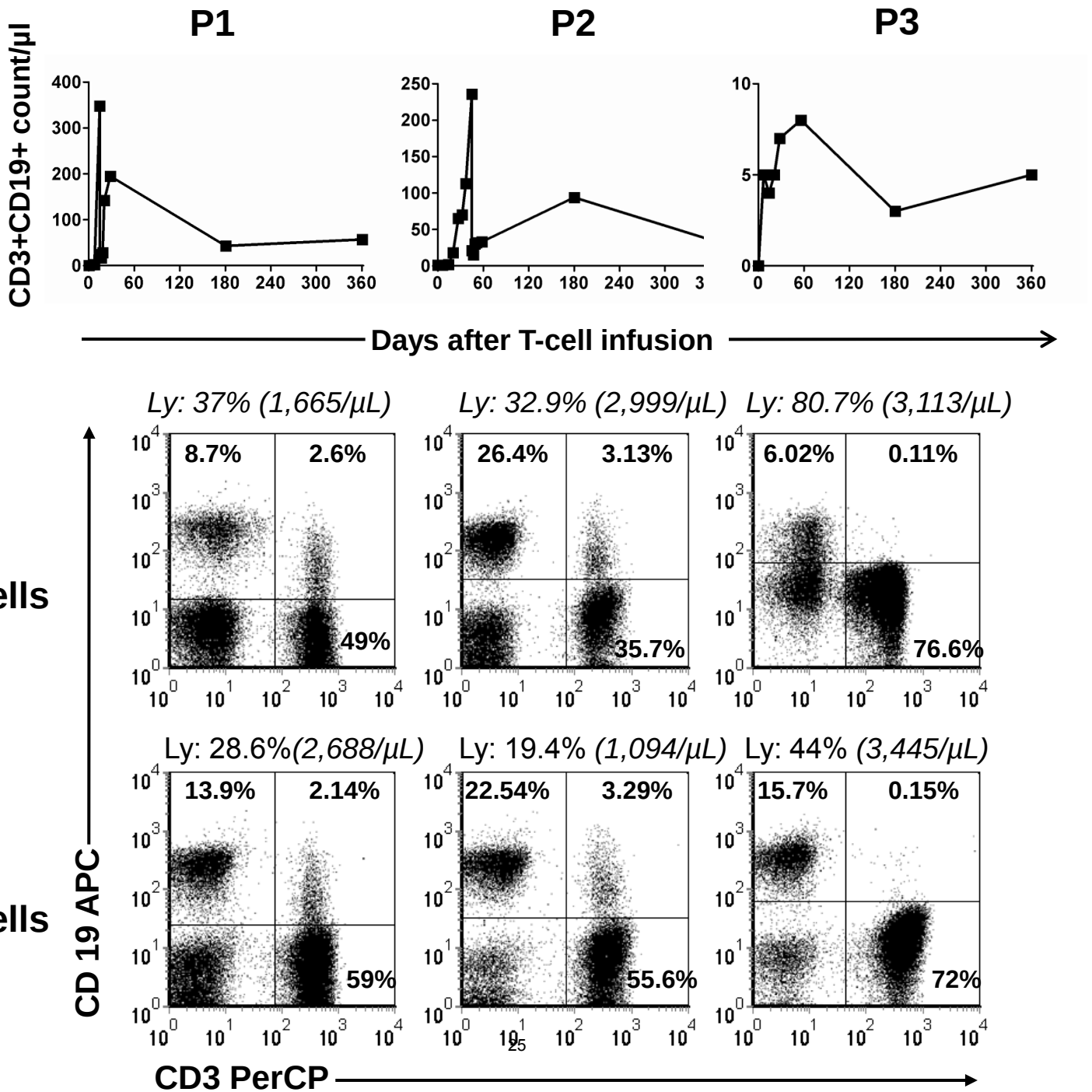

P1
P2
P3
CD3+CD19+ count/µl
Days after T-cell infusion
6 mo
Post T-cells
12 mo
Post T-cells
Ly: 37% (1,665/µL)
Ly: 32.9% (2,999/µL)
Ly: 80.7% (3,113/µL)
Ly: 28.6%(2,688/µL)
Ly: 19.4% (1,094/µL)
Ly: 44% (3,445/µL)
8.7%
2.6%
49%
26.4%
3.13%
35.7%
6.02%
0.11%
76.6%
13.9%
2.14%
59%
22.54%
3.29%
55.6%
15.7%
0.15%
72%
CD 19 APC
CD3 PerCP

Fig S6

Figure S6: Gene-modified (CD3+CD19+) T cells in peripheral blood remain stable for at least 1 year (P1-3); The Figure shows the $CD3^{+}CD19^{+}$ counts per µl of peripheral blood during one year after T cell infusion. In addition, detailed dot plots are shown at 6 and 12 months after T-cell infusion for patients who passed that time point (P1-3). *Ly/µl: lymphocytes per µl of peripheral blood.*

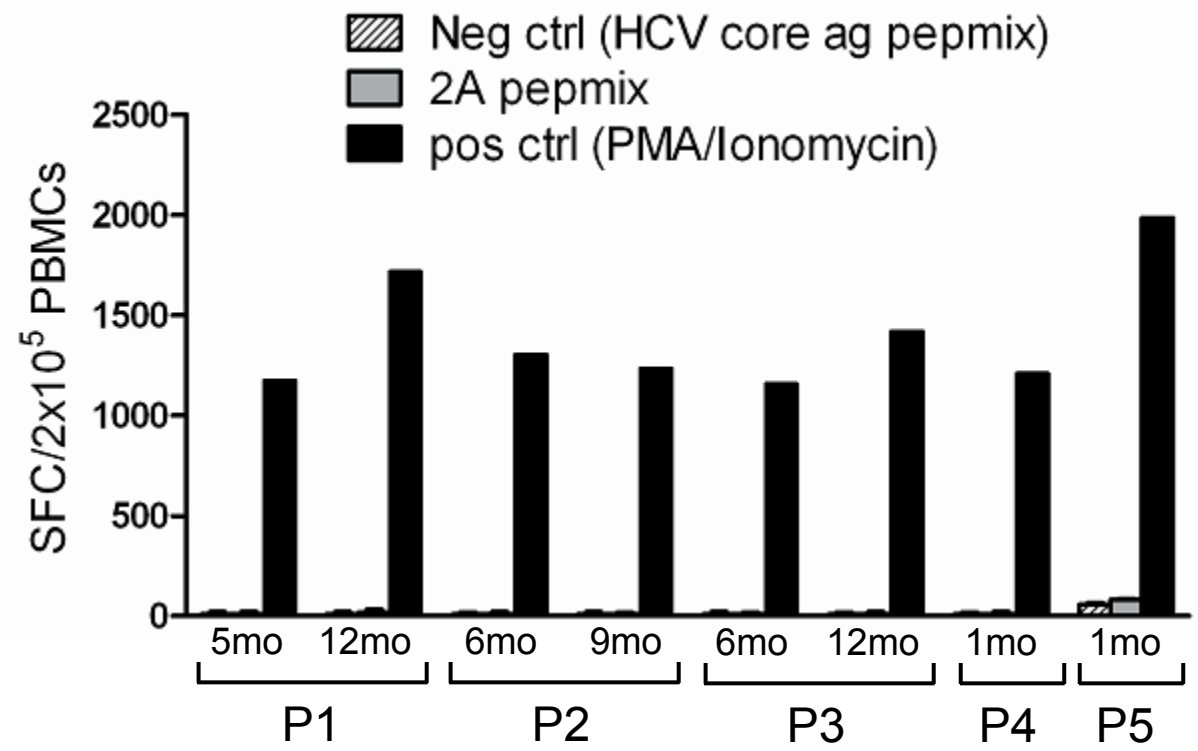

Neg ctrl (HCV core ag pepmix)
2A pepmix
pos ctrl (PMA/Ionomycin)
SFC/2x10^5 PBMCs
2500
2000
1500
1000
500
0
5mo
12mo
6mo
9mo
6mo
12mo
1mo
1mo
P1
P2
P3
P4
P5

Fig S7

Figure S7: Assessing immunity against transgene.

PBMC isolated from P1,2,3,4 and 5 were stimulated with a peptide library representing the sequence of the 2A transgene linker or with an irrelevant peptide mixture (representing HCV core ag) as a negative control and phorbol myristate acetate and ionomycin as a positive control. The number of cells that secreted γ–interferon in response to each stimulus was measured using an Elispot assay.

References

1. Iuliucci JD, Oliver SD, Morley S et al. Intravenous safety and pharmacokinetics of a novel dimerizer drug, AP1903, in healthy volunteers. J Clin Pharmacol. 2001; 41: 870-9.
2. Amrolia PJ, Mucciolo-Casadei G, Huls H et al. Adoptive immunotherapy with allodepleted donor T-cells improves immune reconstitution after haploidentical stem cell transplantation. Blood 2006; 108: 1797-808.
3. Amrolia PJ, Muccioli-Casadei G, Yvon E et al. Selective depletion of donor allo-reactive T-cells without loss of anti-viral or anti-leukemic responses. Blood, 2003; 102:2292-9
4. Akatsuka Y, Martin EG, Madonik A, Barsoukov AA, Hansen JA. Rapid screening of T-cell receptor (TCR) variable gene usage by multiplex PCR: application for assessment of clonal composition. Tissue Antigens. 1999 Feb;53(2):122-34.
5. Donnelly M LL, Luke G, Mehrotra A et al. Analysis of the aphthovirus 2A/2B polyprotein 'cleavage'mechanism indicates not a proteolytic reaction, but a noveltranslational effect : a putative ribosomal 'skip'. J of Gen Virol, 2001; 82:1013-25
6. Quintarelli C, Vera JF, Savoldo B et al. Co-expression of cytokine and suicide genes to enhance the activity and safety of tumor-specific cytotoxic T lymphocytes. Blood 2007; 110: 2793-802
7. Straathof KC, Pule MA, Yotnda P et al. An inducible caspase 9 safety switch for T-cell therapy. Blood 2005; 105: 4247-54.

8. Clackson T, Yang W, Rozamus LW et al. Redesigning an FKBP-ligand interface to generate chemical dimerizers with novel specificity. Proc Natl Acad. Sci U. S. A 1998; 95: 10437-42.
9. Spencer DM, Wandless TJ, Schreiber SL, Crabtree GR. Controlling signal transduction with synthetic ligands. Science 1993; 262: 1019-024.
10. Zhou LJ, Ord DC, Hughes AL, Tedder TF. Structure and domain organization of the CD19 antigen of human, mouse, and guinea pig B lymphocytes. Conservation of the extensive cytoplasmic domain. J Immunol. 1991; 147: 1424-32.
11. Tey SK, Dotti G, Rooney CM, Heslop HE, Brenner MK. Inducible caspase 9 suicide gene to improve the safety of allodepleted T cells after haploidentical stem cell transplantation. Biol Blood Marrow Transplant 2007; 13: 913-24.